

What we claim is:

1. An isolated polynucleotide sequence encoding a chimeric TNF α , comprising a first nucleotide sequence encoding a domain or subdomain of a tumor necrosis factor ligand other than TNF α , wherein the encoded domain or subdomain replaces a cleavage site of native TNF α , and a second nucleotide sequence encoding a domain or subdomain of native TNF α that binds to a TNF α receptor.
2. An isolated polynucleotide sequence encoding a chimeric TNF α , comprising a first nucleotide sequence encoding domain III or a subdomain of domain III of a tumor necrosis factor ligand other than TNF α , wherein the encoded domain or subdomain replaces a cleavage site of native TNF α , and a second nucleotide sequence encoding a domain or subdomain of native TNF α that binds to a TNF α receptor.
3. The isolated polynucleotide sequence of claim 1 or claim 2 wherein the first nucleotide sequence additionally encodes domain II, or a subdomain of domain II, of the other tumor necrosis factor ligand.
4. The isolated polynucleotide sequence of claims 1, 2 or 3, wherein the first nucleotide sequence additionally encodes domain I, or a subdomain of domain I, of the other tumor necrosis factor ligand.

5. The isolated polynucleotide sequence of claims 1, 2, 3 or 4 wherein the first nucleotide sequence additionally encodes a subdomain of domain IV of the other tumor necrosis factor ligand.
6. The isolated polynucleotide sequence of claim 1 or claim 2, wherein the other tumor necrosis factor ligand is selected from the group consisting of CD154, CD70, Fas ligand and TRAIL.
7. The isolated polynucleotide sequence of claim 1 or claim 2 wherein the second nucleotide sequence encodes domain IV, or a subdomain of domain IV, of native TNF α .
8. The isolated polynucleotide sequence of claim 7 wherein the second nucleotide sequence encodes a subdomain of domain IV of native TNF α that lacks a cleavage site of native TNF α .
9. The isolated polynucleotide sequence of claim 1 or claim 2 wherein the first nucleotide sequence encodes domains I, II and III, or subdomains of one or more of domains I, II and III, of a tumor necrosis factor ligand selected from the group consisting of CD154, CD70, Fas ligand, and TRAIL and the second nucleotide sequence encodes domain IV, or a subdomain of domain IV, of native TNF α .

10. The isolated polynucleotide sequence of claim 9 wherein the first nucleotide sequence encodes domains I, II and III, or subdomains of one or more domains I, II and III, of CD154 and the second nucleotide sequence encodes domain IV, or a subdomain of domain IV, of native TNF α .

11. The isolated polynucleotide sequence of claim 1 or claim 2 wherein the sequence additionally includes a linker domain encoding a peptide of at least one amino acid that links the first nucleotide sequence to the second nucleotide sequence.

12. The isolated polynucleotide sequence of claim 1 or claim 2, wherein the sequence is selected from the group consisting of SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3 and SEQ. ID. NO. 4.

13. The isolated polynucleotide sequence of claim 1 or claim 2 wherein the chimeric TNF α comprises an amino acid sequence selected from the group consisting of SEQ. ID. NO. 5, SEQ. ID. NO. 6, SEQ. ID. NO. 7 and SEQ. ID. NO. 8.

14. A chimeric TNF α , comprising a first domain or subdomain of a tumor necrosis factor ligand other than TNF α , wherein the domain or subdomain replaces a cleavage site of native TNF α , and a second domain or subdomain of native TNF α that binds to a TNF α receptor.

15. A chimeric TNF α , comprising a first domain III of a tumor necrosis factor ligand other than TNF α , wherein the domain or subdomain replaces a cleavage site of native TNF α , and a second domain or subdomain of native TNF α that binds to a TNF α receptor.

16. The chimeric TNF α of claim 14 or claim 15 that is less susceptible to cleavage from the surface of cells than native TNF α .

17. The chimeric TNF α of claim 16, wherein the cleavage rate of the chimeric TNF α is at least 90% less than that of native TNF α .

18. The chimeric TNF α of claim 14 or claim 15, wherein the domain or subdomain further comprises domain II, or a subdomain of domain II, of the other tumor necrosis factor ligand.

19. The chimeric TNF α of claims 14, 15 or 18, wherein the domain or subdomain further comprises domain I, or a subdomain of domain I, of the other tumor necrosis factor ligand.

20. The chimeric TNF α of claims 14, 15, 18 or 19, wherein the domain or subdomain further comprises a subdomain of domain IV of the other tumor necrosis factor ligand.

21. The chimeric TNF α of claim 14 or claim 15, wherein the other tumor necrosis factor ligand is selected from the group consisting of CD154, CD70, Fas ligand and TRAIL.

22. The chimeric TNF α of claim 14 or claim 15, further comprising domain IV, or a subdomain of domain IV, of native TNF α .

23. The chimeric TNF α of claim 22 comprising a subdomain of domain IV of native TNF α that lacks a cleavage site of native TNF α .

24. The chimeric TNF α of claim 14 or claim 15, comprising domains I, II and III, or subdomains of one or more of domains I, II and III, of a tumor necrosis factor ligand selected from the group consisting of CD154, CD70, Fas ligand and TRAIL, and domain IV, or a subdomain of domain IV, of native TNF α .

25. The chimeric TNF α of claim 14 or claim 15, comprising domain I, domain II and domain III, or subdomains of one or more domains I, II and III, of CD154 and domain IV, or a subdomain of domain IV, of native TNF α .

26. The chimeric TNF α of claim 14 or claim 15 additionally comprising a linker domain encoding a peptide of at least one amino acid that links the first domain or subdomain to the second domain or subdomain.

27. An expression vector, comprising the isolated polynucleotide sequence of claim 1.
28. The expression vector of claim 27, wherein the polynucleotide sequence encodes a chimeric TNF α comprising domain III, or a subdomain of domain III, of a tumor necrosis factor ligand selected from the group consisting of CD154, CD70, Fas ligand and TRAIL, and domain IV, or a subdomain of domain IV, of native TNF α .
29. The expression vector of claim 28, further comprising a polynucleotide sequence that encodes domain II, or a subdomain of domain II, of a tumor necrosis factor ligand selected from the group consisting of CD154, CD70, Fas ligand and TRAIL.
30. The expression vector of claim 28 or claim 29, further comprising a polynucleotide sequence that encodes domain I, or a subdomain of domain I, of a tumor necrosis factor ligand selected from the group consisting of CD154, CD70, Fas ligand and TRAIL.
31. The expression vector of claim 28 or claim 29, further comprising a polynucleotide sequence that encodes a subdomain of domain IV of a tumor necrosis factor ligand selected from the group consisting of CD154, CD70, Fas ligand and TRAIL.
32. The expression vector of claim 28, further comprising viral DNA or bacterial DNA.

33. The expression vector of claim 32 wherein said viral DNA is selected from the group consisting of adenoviral DNA or retroviral DNA.

34. The expression vector of claim 32, wherein at least a portion of the vector comprises adenoviral DNA.

35. The expression vector of claim 27, further comprising a promoter region.

36. The expression vector of claim 27, further comprising a polyadenylation signal region.

37. A genetic construct comprising the isolated polynucleotide sequence according to claim 1 or claim 2 operatively linked to a promoter sequence and to a polyadenylation signal sequence.

38. A host cell, comprising an expression vector according to claim 27 or a genetic construct according to claim 37.

39. The host cell of claim 38, wherein the cell is a mammalian cell.

40. The host cell of claim 39, wherein the cell is a tumor cell.

41. The host cell of claim 39, wherein the cell is an antigen presenting cell.

42. A process for producing a chimeric TNF α of claim 14 or claim 15 comprising culturing a host cell of claim 38 under conditions suitable to effect expression of the protein.

43. A method for increasing the concentration of a ligand capable of binding to a TNF α receptor on the surface of a cell, comprising introducing into the cell an isolated polynucleotide sequence encoding a chimeric TNF α according to claim 1 or claim 2, whereby the chimeric TNF α is less susceptible to cleavage from the surface of the cells than a native TNF α .

44. The method of claim 43, wherein the isolated polynucleotide sequence comprises an expression vector according to claim 27 or a genetic construct according to claim 37.

45. The method of claim 44 wherein the cell is a mammalian cell.

46. The method of claim 44 wherein the cell expresses a TNF α receptor on its surface.

47. A method for inducing apoptosis of a cell expressing a TNF α receptor, comprising introducing into the cell an isolated polynucleotide sequence encoding a chimeric TNF α according to claim 1 or claim 2 wherein the chimeric TNF α is expressed on the surface of the cell.

48. A method for inducing activation of an immune system cell, comprising introducing into the cell an isolated polynucleotide sequence encoding a chimeric TNF α according to claim 1 or claim 2 wherein the chimeric TNF α is expressed on the surface of the cell.

49. A method for treating neoplasia in a patient comprising introducing into a neoplastic cell an isolated polynucleotide sequence encoding a chimeric TNF α according to claim 1 or claim 2 wherein the chimeric TNF α is expressed on the surface of the cell.

50. The method of claim 49 further comprising:
obtaining the neoplastic cell from a human patient;
infusing the neoplastic cell back into the patient after having introduced into the cells the polynucleotide sequence encoding the chimeric TNF α .

51. A method of treating neoplasia comprising directly injecting into a tumor bed of a patient an isolated polynucleotide sequence encoding a chimeric TNF α according to claim 1 or claim 2 wherein the chimeric TNF α is expressed in the tumor bed.

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